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Smoking resumption after heart or lung transplantation: a systematic review and suggestions for screening and management

Hofmann, Patrick ; Benden, Christian ; Kohler, Malcolm ; Schuurmans, Macé M

Abstract: Smoking remains the leading cause of preventable disease and death in the developed world and kills half of all long-term users. Smoking resumption after heart or lung transplantation is associated with allograft dysfunction, higher incidence of cancer, and reduced overall survival. Although self-reporting is considered an unreliable method for tobacco use detection, implementing systematic cotinine-based screening has proven challenging. This review examines the prevalence of smoking resumption in thoracic transplant patients, explores the risk factors associated with a post-transplant smoking resumption and discusses the currently available smoking cessation interventions for transplant patients.

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Correlates and Outcomes of Posttransplant Smoking in Solid Organ Transplant Recipients: A Systematic Literature Review and Meta-Analysis

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Background. Despite smoking being an absolute or relative contraindication for transplantation, about 11% to 40% of all patients continue or resume smoking posttransplant. This systematic review with meta-analysis investigated the correlates and outcomes associated with smoking after solid organ transplantation. **Methods.** We searched PubMed, EMBASE, CINAHL, and PsycINFO from inception until January 2016, using state-of-the art methodology. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were computed for correlates/outcomes investigated 5 times or more. **Results.** Seventy-three studies (43 in kidney, 17 in heart, 12 in liver, 1 in lung transplantation) investigated 95 correlates and 24 outcomes, of which 6 correlates and 4 outcomes could be included in the meta-analysis. The odds of smoking posttransplant were 1.33 times higher in men (95% CI, 1.12-1.57). Older individuals were significantly less likely to smoke (OR, 0.48; 95% CI, 0.38-0.62), as were patients with a higher body mass index (OR, 0.68; 95% CI, 0.52-0.89). Hypertension (OR, 1.16; 95% CI, 0.77-1.75), diabetes mellitus (OR, 0.52; 95% CI, 0.15-1.78), and having a history of cardiovascular disease (OR, 0.92; 95% CI, 0.77-1.09) were not significant correlates. Posttransplant smokers had higher odds of newly developed posttransplant cardiovascular disease (OR, 1.41; 95% CI, 1.02-1.95), nonskin malignancies (OR, 2.58; 95% CI, 1.26-5.29), a shorter patient survival time (OR, 0.59; 95% CI, 0.44-0.79), and higher odds of mortality (OR, 1.74; 95% CI, 1.21-2.48). **Conclusions.** Posttransplant smoking is associated with poor outcomes. Our results might help clinicians to understand which patients are more likely to smoke posttransplant, guide interventional approaches, and provide recommendations for future research.

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Tobacco use, present in about 1 in 5 people aged 15 years or older in the general population,[1,2] is one of the main risk factors for a number of chronic diseases, including cancer, pulmonary, and cardiovascular diseases. It kills nearly 6 million people worldwide each year and continues to be the leading global cause of preventable death.[1-4]

For solid organ transplant patients, smoking may be even more harmful. Due to the need for lifelong immunosuppressive medication intake, transplant recipients are already prone to infections, cancer and cardiovascular disease, and health risks might be even further increased when smoking. Indeed, 2 reviews found that smoking significantly increases the risk of renal fibrosis, malignancy, death-censored allograft loss, and patient death in kidney transplant patients[5,6]; hepatic artery thrombosis, biliary complications, and malignancy in liver transplant patients[6]; and coronary atherosclerosis, malignancy, renal dysfunction, all-cause, and cardiac death in heart transplant patients.[6] Corbett et al,[6] however, did not conduct a systematic review, and neither reviews used meta-analytic techniques. They also did not make a clear distinction between pretransplant and posttransplant smoking. Moreover,

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without calculating effect sizes, it is hard to appreciate the true association of posttransplant smoking on clinical outcomes.

In an attempt to prevent these adverse effects of posttransplant smoking, international consensus guidelines recommend considering active tobacco smoking or tobacco use within the last 6 months as a contraindication for lung and heart transplantation,[7-9] and strongly advise smoking cessation before kidney and liver transplantation.[10-12] However, studies show that a substantial number of transplant patients continue or resume smoking posttransplant. More specifically, a meta-analysis of 49 studies showed 3.4 cases of tobacco use per 100 transplant patients per year (adjusted for follow-up duration).[13] A more recent review showed that smoking recidivism rates after transplantation vary between 11% and 40%, depending on the definition of smoking and smoking detection methods used.[6]

Bearing in mind the high prevalence of posttransplant smoking, it is of critical importance to understand which individuals are at the greatest risk for sustained or resumed smoking, so that timely interventions can be implemented. However, to date, few studies investigated correlates of posttransplant smoking. In their systematic review, Dew and colleagues[13] found that pretransplant substance use (ie, tobacco, alcohol, and illicit drug use) was strongly correlated with posttransplant substance use ($r = 0.62$; 95% confidence interval [95% CI], 0.22-0.84). However, the authors did not look at tobacco use separately, and given that the literature search was completed in 2005, it is possible that more recent evidence provides additional insights on correlates of posttransplant smoking.

Considering these gaps, we therefore aimed to perform a systematic literature review and meta-analysis to identify and quantitatively synthesize available evidence on correlates and outcomes of posttransplant smoking in adult single lung, heart, liver, and kidney organ transplant patients.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted in line with the methodology outlined in the Center for Reviews and Dissemination handbook (UK),[14] and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for data reporting.[15] Reviews on correlates and outcomes of posttransplant alcohol use, medication adherence, and physical activity were conducted in parallel as part of the B-SERIOUS research program (Brocher Foundation-funded grant to develop a Solid organ transplant Endpoint model on Relationships between Influencing factors and Outcomes of transplant Self-management behaviors).

The protocol was registered in the PROSPERO database (registration number CRD42015003333).[16]

Definition of Smoking

In this review, smoking is defined as the active inhalation of smoke of burning tobacco encased in cigarettes, pipes, and cigars, measured by self-report or biochemical validation of tobacco exposure, after solid organ transplantation. Thus, this review did not include studies on electronic cigarettes, secondhand smoke, smokeless tobacco, and smoking before transplantation, or studies in which the distinction between pretransplant and posttransplant smoking was not clear.

Search Strategy

We originally conducted electronic searches of PubMed, EMBASE.COM, EBSCOhost, CINAHL, and Ovid PsycINFO, from database inception until June 29, 2012. Searches were updated in January 2016, covering the period of June 2012 to January 1, 2016. The search string was first developed for PubMed in close collaboration with a health sciences librarian (M.L.K.) and translated afterward for use in the other databases. All database search strings contained both controlled vocabulary and free text words representing the concepts of smoking and solid organ transplantation. The PubMed search string is shown in Table 1. The other database search strings are available from the researchers upon request. In addition to the database searches, the reference sections of the eligible articles were searched to identify additional studies.

TABLE 1.

Detailed search string used in the electronic database PubMed

PubMed (1323 results on January 1, 2016)
(("Heart Transplantation"(MeSH:noexp]) OR (heart transplant*(Tiab]) OR (cardiac transplant*(Tiab]) OR (heart graft*(Tiab]) OR (heart allograft*(TiabTiab]) OR (cardiac allograft*(Tiab] OR (cardiothoracic transplant*(Tiab] OR (thoracic transplant*(Tiab] OR (Cardiac Graft* (Tiab]) OR ("Kidney Transplantation"(MeSH]) OR (kidney transplant*(Tiab]) OR (renal transplant*(Tiab]) OR (kidney graft*(Tiab]) OR (kidney allograft*(Tiab]) OR (renal allograft*(Tiab] OR (Renal Graft* (Tiab])) OR ("Liver Transplantation"(MeSH]) OR (liver transplant*(Tiab]) OR (hepatic transplant*(Tiab]) OR (liver graft*(Tiab]) OR (liver allograft*(Tiab]) OR (hepatic allograft*(Tiab] OR (Hepatic Graft* (Tiab]) OR ("Lung Transplantation"(MeSH:noexp]) OR (lung transplant*(Tiab]) OR (lung graft*(Tiab]) OR (lung allograft*(Tiab]) OR (pulmonary transplant*(Tiab] OR (Pulmonary Graft* (Tiab]) OR ("Organ Transplantation"(MeSH:noexp]) OR (solid organ*(Tiab]) OR (organ transplant*(Tiab])) AND (((("Smoking"(MeSH]) OR (smoking(Tiab]) OR (smoker*(Tiab]) OR (exsmoker*(Tiab]) OR (ex smoker*(Tiab]) OR (cigarette*(Tiab]) OR (tobacco*(Tiab]) OR ("Smoking Cessation"(MeSH]) OR ("Cotinine"(MeSH]) OR (cotinine(Tiab]) OR ("Tobacco Use Disorder"(MeSH]) OR ("Tobacco"(MeSH:noexp]) OR (nonsmoker*(Tiab]) OR (non smoker*(Tiab]) OR (nonsmoking(Tiab]) OR (non smoking(Tiab]) OR ("Tobacco, Smokeless"(MeSH]) OR (smokeless tobacco(Tiab]) OR (oral tobacco(Tiab]) OR (chew*(Tiab]) OR (snuff(Tiab]) OR ("Tobacco Use Cessation"(MeSH:noexp]) OR (moist tobacco(Tiab]) OR (snus(Tiab]))) OR (((((((((((((((((((((((((((((((((("Nicotine"(MeSH])) OR ("Tobacco Use Cessation Products"(MeSH])) OR (nicotine(Tiab])) OR (nicorette(Tiab])) OR (nicotinelle(Tiab])) OR (electronic cigarette*(Tiab])) OR (cigar(Tiab] OR cigars(Tiab])) OR ("Cannabis"(MeSH])) OR (cannabis(Tiab])) OR (marijuana(Tiab])) OR (marihuana(Tiab])) OR (ganja(Tiab])) OR (hashish(Tiab])) OR (bhang(Tiab])) OR ("Marijuana Smoking"(MeSH])) OR ("Marijuana Abuse"(MeSH])) OR (hookah(Tiab])) OR (narghile(Tiab])) OR (bidi(Tiab] OR bidis(Tiab])) OR (shisha(Tiab])) OR (waterpipe*(Tiab])) OR (water pipe*(Tiab])) OR (chillum(Tiab])) OR (sheisha(Tiab])) OR (qalyan(Tiab])) OR ("Tobacco Smoke Pollution"(MeSH])) OR (passive smok*(Tiab])) OR (secondhand smok*(Tiab])) OR (second hand smok*(Tiab])) OR (involuntary smok*(Tiab])) OR (goza(Tiab])) OR (argileh(Tiab])) OR (narkeela(Tiab])) OR (hubble bubble(Tiab])) OR (hooka(Tiab])) OR (hukka(Tiab])))

MeSH, Medical Subject Heading; Tiab, Title/Abstract.

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Inclusion and Exclusion Criteria

To be included, reported studies had to meet all of the following criteria: (1) original or primary quantitative research or mixed methods research; (2) conducted in adult single lung, heart, liver, or kidney transplant patients; (3) measured posttransplant smoking; (4) assessed the association between posttransplant smoking and correlates and/or clinical, economic, and quality of life outcomes; (5) included information needed to allow effect size calculation (at a minimum, the sample size, information on the direction of the association, and a *P* value less or more than a specified value [eg, $P < 0.05$; $P > 0.01$]); (6) reported in English, Dutch, German, French, Portuguese, Italian, or Spanish; and (7) full text available.

The following papers were excluded: (1) papers that did not report results from an original quantitative or mixed method study (eg, results from qualitative research only, review, editorial, dissertation, book chapter, case studies, or case series with no descriptive data), (2) abstracts not accompanied by a full paper, (3) studies on children or adolescents aged 18 years or younger, (3) studies on combined organ transplant populations (eg, liver-kidney), (4) studies on other types of tissue or organ transplantation (eg, stem cell or pancreas transplantation), and (5) quantitative studies focusing on a different topic or not addressing correlates or outcomes of posttransplant smoking.

Study Selection

First, pairs of researchers (N.D., H.B., M.K., and S.E.) independently screened all titles and abstracts against the inclusion and exclusion criteria to identify potentially relevant papers. Second, the full article of potentially relevant abstracts was obtained and evaluated for eligibility by the same researchers. Comparisons were made afterward and any scoring discrepancies were resolved. A third researcher (F.D.) was involved in cases of disagreement. In case of multiple publications reporting similar results from the same patient samples (ie, companion papers), data were extracted from the most recent publication only or from the article with the largest sample size or most complete data set.

Data Extraction

We extracted the following data from each study using a data extraction form developed for the purpose of this review: first author name, journal, publication year and language, continent and country where the study was conducted, funding source, study design, sample characteristics (eg, sample design, sample size, sample size calculation, transplant population, age, sex, race, time posttransplant), details on the posttransplant smoking behavior (eg, definition of smoking, types of smoking, smoking measurement, quantification of smoking, and prevalence of posttransplant smoking), and whether researchers used a theoretical or conceptual framework. Further, we tabulated all the correlates and outcomes studied. The correlates were classified according to the World Health Organization taxonomy originally designed for medication adherence into the following 5 dimensions: socioeconomic-, patient-, condition-, treatment-, and healthcare team- and system-related factors.[17] Outcomes were divided into clinical, economic, and quality of life outcomes. Outcomes were defined as conditions that are not yet present at time of transplantation, but develop posttransplant. If conditions (eg, hypertension, cardiovascular disease) were present before or at the time of transplantation, they were classified as condition-related factors. For both correlates and outcomes, we extracted the descriptive results, inferential analysis results and effect sizes if available in the article.

Data were extracted independently by 2 researchers and compared afterward. Inconsistencies were resolved by consensus or consultation with a third researcher.

Quality Assessment

Two researchers rated each study independently on 14 components of methodological quality, using an adapted version of a checklist developed by Harlein and colleagues.[18,19] The quality criteria were related to the definitions used, research design, sampling strategies, sample sizes, psychometric properties of the instruments, methods for data analysis, completeness of data reporting, and reproducibility of the study. To determine whether the sample size was appropriate, we checked whether there was an a priori sample size justification. If not, we checked if there were at least 104 + m subjects (where m is the number of independent variables) for testing individual predictors or 50 + 8 m subjects for testing multivariate analysis.[20] In the case of disagreement, articles were reviewed again and discussed until consensus was reached. Because not all quality criteria were applicable to all studies, we did not calculate total scores.

Data Analysis

Descriptive statistics were calculated to describe the characteristics of the studies included. Effect sizes, expressed as odds ratios (ORs) with 95% CIs, were extracted or calculated for correlates or outcomes investigated by a sufficient numbers of studies (ie, ≥ 5). The OR was calculated directly when group frequencies were reported. If studies reported 3 groups of smokers (ie, nonsmokers, past smokers, and current smokers), nonsmokers and past smokers were combined and compared with the current smokers, because we were particularly interested in correlates and outcomes of active posttransplant smoking. If only medians and interquartile ranges were reported for each of the 3 groups, with 1 single *P* value comparing the 3 groups simultaneously, no OR could be calculated. If frequencies were not reported, the OR was calculated indirectly using the descriptive or inferential statistics reported. The web-based Practical Meta-Analysis Effect Size Calculator was used to facilitate the calculation of ORs.[21] For the purpose of this meta-analysis, posttransplant smokers were always included in the exposed group irrespective of duration or intensity of smoking posttransplant.

A random-effects model was used to calculate the summary OR across all contributing studies using the Comprehensive Meta-Analysis software (version 2.2, Biostat, Inc., Englewood, NJ).[22] Random effects models account for any observed heterogeneity regardless of whether the heterogeneity is statistically significant. For each statistically significant average effect size, we calculated the classic failsafe N to estimate the impact of publication bias. The most commonly suspected publication bias is the tendency to only publish studies with statistically significant results. The classic failsafe N is the number of nonsignificant studies that would be needed to make the combined effect size statistically insignificant. We also calculated Cochran Q to determine whether there was significant variability in effect sizes across studies.

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Given that the Q test, however, has limited power to detect significant heterogeneity when the number of studies is small, we also calculated indices summarizing heterogeneity, that is, the τ^2 (the variance of the true effect sizes) and I^2 (the percentage of variations across studies due to heterogeneity rather than chance).[23]

Correlates and outcomes studied less than 5 times were not included in the meta-analysis and are summarized in bar charts. The bar charts represent the number of papers that studied a specific factor and whether the association between the correlate/outcome and posttransplant smoking was significant or nonsignificant.

RESULTS

Study Selection

Figure 1 shows the number of papers excluded at each stage of the review. Starting from 4223 references, 73 papers met the inclusion criteria.

Study Characteristics

Table 2 summarizes the study characteristics. Among the 73 included papers, 43 studies focused on kidney, 17 on heart, 12 on liver, and 1 on lung transplant patients. Most studies were conducted in Europe (n = 48, 65.8%) and used a prospective observational design (n = 26, 35.6%). The median sample size was 185 (range, 34-41705). The mean age of participants was 48.5 years (range, 13-84 years).

There was a wide variation in reported rates of posttransplant smoking (range, 1.0-73.0%; mean, 24.27%). In terms of assessment, only 40 studies (54.8%) reported how they measured smoking, with patient self-report being the most common measurement method (n = 26, ie, 35.6%) and only 6 studies using biomarkers of tobacco exposure (eg, serum and urinary cotinine levels, carboxyhemoglobin levels).[24-27] Only 22 studies (28.8%) mentioned smoking type, of which the majority (n = 21, 95.5%) referred to cigarettes. Most studies looked at sustained smoking or relapse, whereas only 1 study investigated new-onset posttransplant smoking exclusively (excluding patients with a history of smoking pretransplant).[28]

Quality Assessment

Figure 2 shows the results of the quality assessment. The majority of studies used appropriate sample sizes (n = 45, 61.6% for univariable tests, n = 35, 47.9% for multivariable tests) and data analysis methods (n = 60, 82.2%). Only 28 studies (38.4%) used a clear definition for smoking; 12 studies (16.4%) defined the correlates investigated; 26 studies (35.6%) used a prospective design; 13 studies (17.8%) described their data collection procedures in a comprehensive way; and, respectively, 3 (4.1%) and 8 studies (11.0%) fully or partially reported on the psychometric properties of the instruments used. Moreover, none of the studies described the methods in ways that they could be replicated accurately.

Correlates of Posttransplant Smoking

Included studies identified 95 correlates of posttransplant smoking, of which 89 were studied less than 5 times (presented as bar charts, see Figures 3-6), consisting of 8

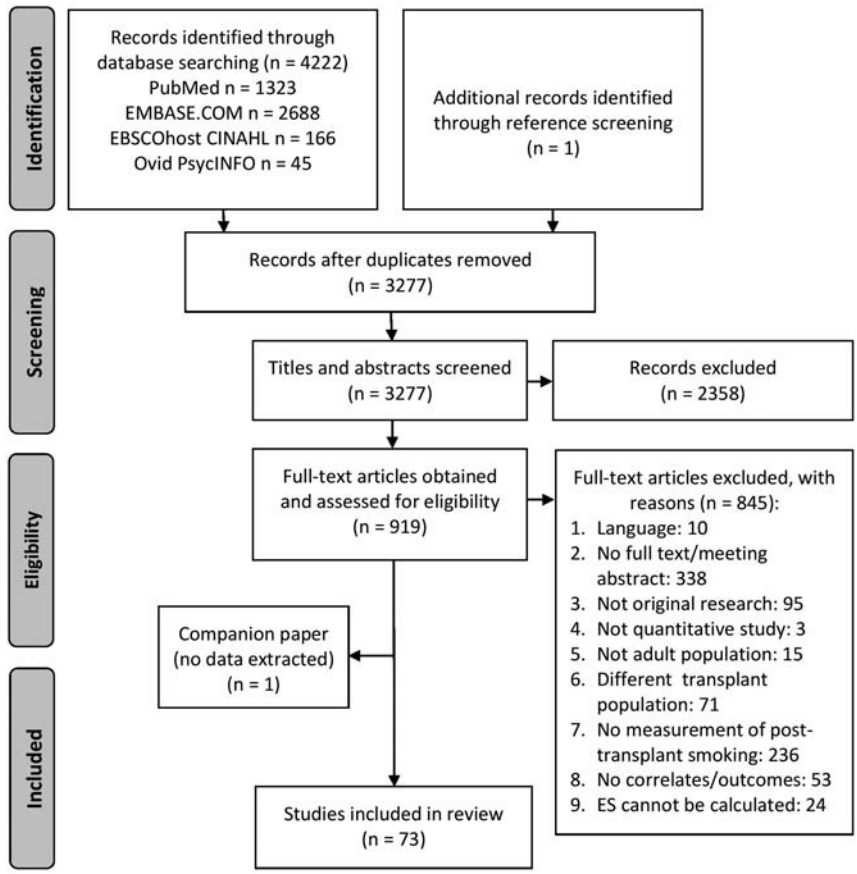

FIGURE 1. Flow chart of study selection process (adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart guidelines).

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TABLE 2.

Characteristics of included studies (n = 73)

Characteristics	Total (n = 73)	Type of organ transplant			
		Kidney (n = 43)	Heart (n = 17)	Liver (n = 12)	Lung (n = 1)
Study location					
Europe	48 (65.8%)	29 (67.4%)	11 (64.7%)	8 (66.7%)	
North America	16 (21.9%)	7 (16.3%)	6 (35.3%)	2 (16.7%)	1 (100%)
Asia	5 (6.8%)	4 (9.3%)		1 (8.3%)	
Australia	3 (4.1%)	3 (7.0%)			
South America	1 (1.4%)			1 (8.3%)	
Study design					
Prospective observational	26 (35.6)	13 (30.2%)	9 (53.0%)	4 (33.3%)	
Cross-sectional	20 (27.4)	13 (30.2%)	4 (23.5%)	3 (25.0%)	
Retrospective observational	23 (31.5)	13 (30.2%)	4 (23.5%)	5 (41.7%)	1 (100%)
Case-control	3 (4.1)	3 (7.0%)			
Other	1 (1.4)	1 (2.3%)			
Sample size					
Mean	936	1465	152	227	34
Median	185	231	115	175	
Range	34-41705	40-41705	59-381	59-465	
Race/ethnicity (mean prevalence in included studies)					
Caucasian/White	81.00%	82.64%	79.70%	78.05%	
African descent/Black	16.88%	19.86%	24.10%	5.20%	
Hispanic/Latinos	1.40%	0.00	2.00%	1.50%	
Native American/American Indian, y	0.25%	0.00	0.00	0.50%	
Asian/Pacific Islanders	0.50%	0.00	0.00	1.00%	
Mean % male sex	67.16%	62.92%	78.42%	68.10%	64.70%
Mean age at transplantation, y	48.50	47.09	50.07	52.83	53.90
SD	11.29	11.66	11.09	10.42	6.67
Range	13-84	13-84	13-83	17-76	
Time posttransplant, y					
Mean	5.96	5.42	5.94	8.80	
SD	3.15	3.02	3.78	2.43	
Median	6.74	6.00		7.78	
Prevalence of posttransplant smoking					
Mean	24.27%	23.84%	25.33%	25.27%	14.7%
SD	13.01	14.44	12.60	8.36	
Median	22.20%	22.00%	23.30%	21.24%	
Range	1.00-73.00%	1.00-73.00%	9.20-52.00%	16.50-37.93%	

IQR, Interquartile range.

socioeconomic-related factors (Figure 3), 16 patient-related factors (Figure 4), 49 condition-related factors (Figure 5), and 16 treatment-related factors (Figure 6). None of the studies examined the relationship between posttransplant smoking and healthcare team/system-related factors.

Average effect size estimates could be calculated for 6 correlates (Table 3, Figure 7). The odds of posttransplant smoking was 1.33 times higher in men than in women (95% CI, 1.12-1.57; $P = 0.001$). Older individuals had significantly lower odds than those who were younger. For each year increase in age, the odds of smoking decreased by 0.48 (95% CI, 0.38-0.62; $P < 0.001$). For body mass index (BMI), evidence suggests that for every 1 unit increase (kg/m^2) in BMI, the odds of smoking decreased by 0.68 (95% CI, 0.52-0.89; $P = 0.006$). Pooling data from 7 studies, it was shown that having hypertension or being treated with antihypertensive drugs was not significantly associated with posttransplant smoking (OR, 1.16; 95% CI, 0.77-1.75; $P = 0.467$). The same applied for diabetes mellitus (already present at time of transplantation or unclear if newly developed) (OR, 0.52; 95% CI, 0.15-1.78; $P = 0.301$) (based on 7 studies), and a history of cardiovascular disease (OR, 0.92; 95% CI, 0.77-1.09; $P = 0.308$) (based on 5 studies).

Examination of the variability in study effect sizes for correlates reported in terms of I^2 in Table 3 indicate low heterogeneity for sex ($I^2 = 24.42\%$) and history of cardiovascular disease ($I^2 = 0\%$); moderate heterogeneity for BMI ($I^2 = 50.12\%$); and high levels of heterogeneity for age ($I^2 = 71.55\%$), hypertension ($I^2 = 72.94\%$), and diabetes ($I^2 = 97.56\%$). In particular, the directions of the ORs for hypertension and diabetes were inconsistent across the studies (ie, ORs >1 and <1).

Outcomes of Posttransplant Smoking

Included studies examined 24 outcomes of posttransplant smoking, of which 20 were studied less than 5 times (Figure 8). There was only 1 study investigating the association with health-related quality of life and no studies investigating economic outcomes.

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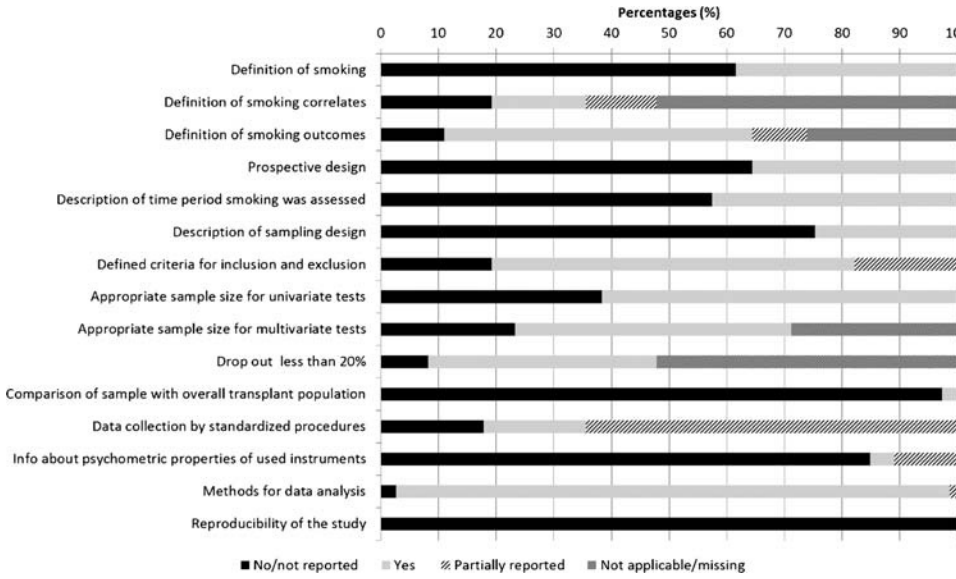

FIGURE 2. Quality assessment.

Average effect size estimates could be calculated for 4 outcomes (Table 3, Figure 7). Across 9 studies, our meta-analysis showed that the odds of having cardiovascular disease (ie, new onset disease not present at time of transplantation) were 1.41 times higher than that of nonsmokers (OR, 1.41; 95% CI, 1.02-1.95; $P = 0.036$). Based on 6 studies, the odds ratio for the association between posttransplant smoking and nonskin malignancies was 2.58 (95% CI, 1.26-5.29; $P = 0.01$). The pooled results from 5 and 8 studies showed a statistically significant association of posttransplant smoking with patient survival time (OR, 0.59; 95% CI, 0.44-0.79; $P < 0.001$) and patient mortality (OR, 1.74; 95% CI, 1.21-2.48; $P = 0.003$), respectively.

Assessment of heterogeneity of study effect sizes for outcomes yields a low I^2 value of 38.77% for cardiovascular disease, moderate I^2 value of 50.59% for patient survival time, and high I^2 values of 73.68% and 83.38% for nonskin malignancies and patient mortality, respectively (Table 3). Except for 1 study on nonskin malignancies and 1 study on patient mortality, the directions of the associations across studies were consistent.

DISCUSSION

This systematic review and meta-analysis comprehensively summarized the state of the art on correlates of pos-transplant smoking for the first time. It is also the first investigation that synthesized study findings on the association of posttransplant smoking with various clinical outcomes in single adult lung, heart, liver, and kidney transplant patients. This is useful given the continued challenge to identify modifiable risk factors to improve posttransplant outcomes. The results of this meta-analysis may inform transplant clinicians which patients are more likely to smoke posttransplant and provide some recommendations for future research in this area.

Surprisingly enough, of the 90 correlates abstracted from the included papers, we could only calculate pooled effect sizes for 6 of them. More specifically, we revealed that male patients, younger patients, and patients with a lower BMI were more likely to be smokers. Hypertension, diabetes mellitus, and a history of cardiovascular disease were not significantly associated with posttransplant smoking. However, it is important to be cautious about drawing conclusions for hypertension and

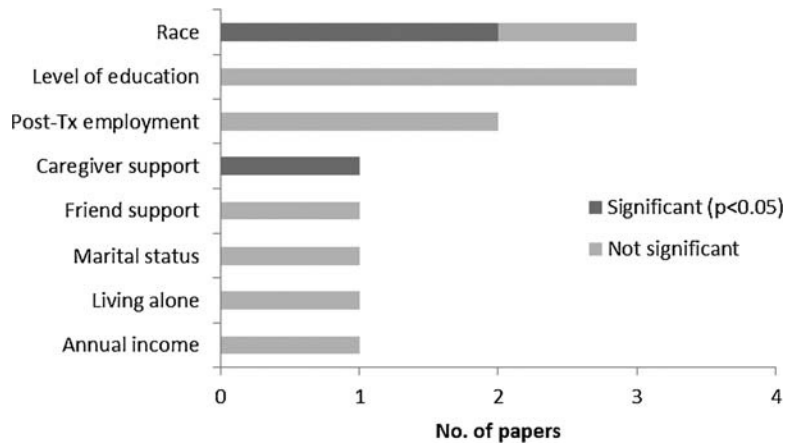

FIGURE 3. Socioeconomic-related correlates of posttransplant smoking assessed by 1 to 4 studies.

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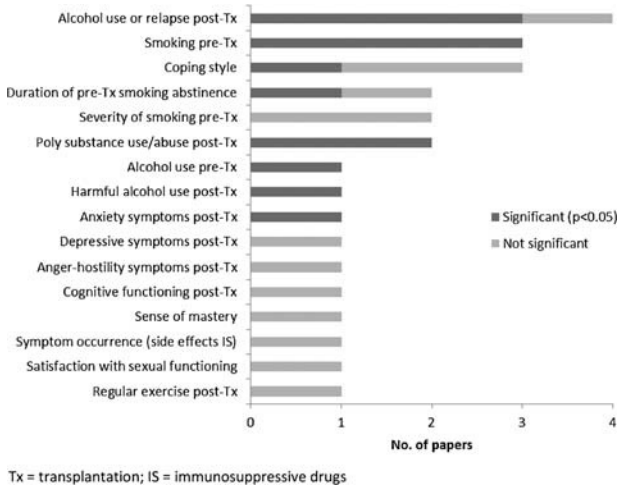

FIGURE 4. Patient-related correlates of posttransplant smoking assessed by 1 to 4 studies.

diabetes, because the directions of the ORs were inconsistent across the studies, in addition to high I^2 values.

The finding that male patients are more likely to smoke posttransplant is in line with the World Health Organization findings showing that men smoke at 5 times the rate of women (the average rates are 36% and 7%, respectively).[56] Globally, however, the gap between men's and women's smoking rates is becoming smaller. As society became more tolerant of women who smoke and women's economic resources are increasing, the tobacco industry has been targeting women through advertisements promoting cigarettes as a symbol of freedom, emancipation, beauty, and prestige.[57,58] So also in transplantation, despite men being more prone to posttransplant smoking, the rise of smoking among women needs to be carefully followed.

From our results, it also appeared that older patients were less likely to smoke than younger patients. A hypothesis might be that older transplant patients experience more health problems, including smoking-related illnesses, and therefore are more likely to stop smoking, yet this merits further investigation. Another possibility is that older patients already died because of smoking-related illnesses and were subsequently not included in the analyses (ie, survival bias).

For BMI, we found that patients with a higher BMI were significantly less likely to smoke. On the one hand, this is not surprising because smokers tend to be leaner than nonsmokers and concerns over weight gain are often a reason why individuals are reluctant to stop smoking.[59,60] On the other hand, one would expect that unhealthy behaviors, such as smoking, unhealthy eating, and physical inactivity, go hand in hand. Also, in the general population, the association between BMI and smoking is complex and not completely understood, and published studies yielded conflicting results.[61] More studies are needed to explore possible causal mechanisms.

Hypertension was not significantly associated with posttransplant smoking. This should come as no surprise because although smoking can cause acute blood pressure elevation through the stimulation of the sympathetic nervous system,[62] chronic smoking has not been conclusively shown to cause high blood pressure in the general population.[63] The lack of an association between diabetes mellitus and posttransplant smoking, on the other hand, contradicts evidence in other populations, showing that smokers are 30% to 40% more likely to develop type 2 diabetes than nonsmokers.[64] It might be that an association in this meta-analysis was not found because intensity and duration of smoking (including pretransplant smoking) were not taken into account. As indicated earlier, it must also be noted that there was a significant degree of heterogeneity among the studies for hypertension and diabetes, making it difficult to draw any firm conclusions. When comparing these different studies, differences can be observed, with a wide variety between study designs used, smoking definitions, and smoking assessment methods, possibly explaining the observed heterogeneity. For 3 of the 7 studies on diabetes, it was also not clear whether diabetes was already present at time of transplantation or newly developed after transplantation.

Having a history of cardiovascular disease was also not significantly associated with posttransplant smoking. In contrast to hypertension and diabetes, there was no heterogeneity among the studies. The lack of a significant association is difficult to explain. One would assume that patients who have a history of cardiovascular disease are probably more likely to be the ones who smoked pretransplant, and 3 studies included in this review showed that pretransplant smoking was associated with posttransplant smoking (Figure 4). On the other hand, it is possible that having a history of cardiovascular disease is a good motivator to maintain smoking abstinence. Additional research examining the association between having a history of cardiovascular disease and posttransplant smoking is needed.

For the remaining 89 correlates, no effect sizes could be calculated. Most of these factors were investigated only once or twice and focused largely on condition-related factors, whereas healthcare team and system-related factors were not studied at all. Yet, smoking is a behavioral process strongly influenced by the environment in which the patient lives, including the healthcare practices and systems. Thus, from a behavioral perspective, healthcare team and system-related factors should be studied more. The general paucity of studies examining relevant factors is probably due to a lack of theoretical underpinnings in the included studies. Nevertheless, theoretical or conceptual models, like "the Integrated Model of Behavioral Prediction of Fishbein"[65] or "the conceptual framework of the International Tobacco Control Policy Evaluation Project"[66] are valuable in developing more targeted research questions, in identifying variables to study, and in interpreting research results.

Of the 24 outcomes abstracted from the included papers, we could only calculate pooled effect sizes for 4 of them, that is, cardiovascular disease, nonskin malignancies, patient survival time, and patient mortality. Our results suggest that posttransplant smoking is statistically significantly associated with all 4 outcomes, which is in line with the wide acknowledgment that cigarette smoking is a major risk factor for cardiovascular disease, cancer, and mortality in the general population. However, given that smoking globally contributes to the burden of over 200 diseases, it is remarkable that few studies (ie, less than 5 studies) explored the effects of posttransplant smoking on other outcomes, such as graft loss, stroke, pulmonary diseases, kidney function, osteoporosis, skin problems, and so on. On the other hand, the fact that 73 studies examined correlates/outcomes of posttransplant

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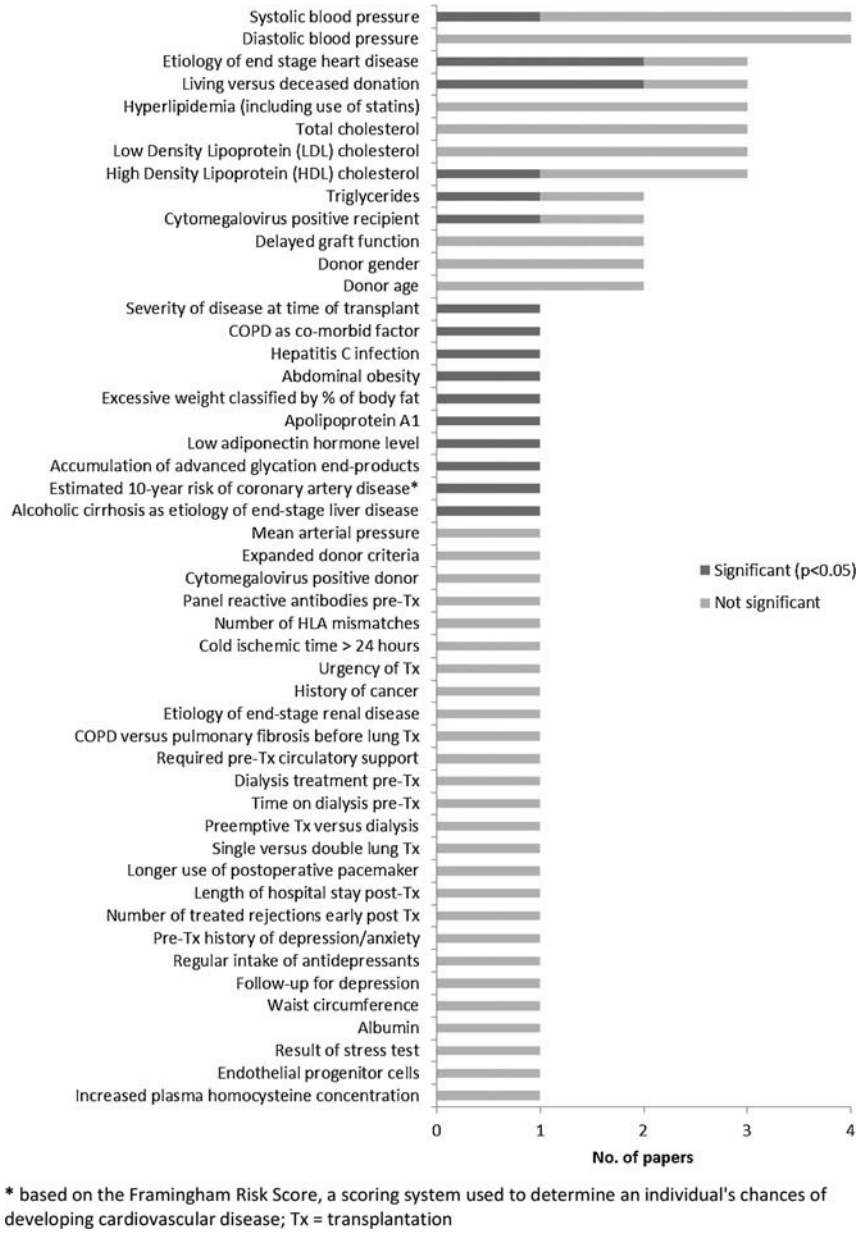

FIGURE 5. Condition-related correlates of posttransplant smoking assessed by 1 to 4 studies.

smoking indicates that not only pretransplant smoking but also smoking after transplantation is increasingly recognized as being important. For a long time, it was assumed that transplant patients did not smoke after having received the precious gift of life. However, we should not forget that smoking is an addiction, hence relapse after transplantation is always possible.[67] Smoking relapse after smoke-free periods is not typical for transplant patients, but reflects the cyclic process of smoking-quitting relapse also observed in the general population.

Apart from the fact that few pooled effect sizes could be calculated for both correlates and outcomes, despite the multitude of factors having been explored, some results from the quality assessment also merit some further reflection. First, most studies did not provide a definition of smoking, and for those that did, the definition was not consistent. For example, some defined smoking as "smoking 7 or more cigarettes per week,"[40] while others simply defined it as current smoking, regardless of the intensity or duration of smoking.[68] Future research should specify the type and "dose" of smoking over a specific time period (eg, posttransplant or lifetime). Second, 47 studies (64.4%) did not use a prospective observational design, hence conclusions cannot be made about causality. Third, most studies used self-reporting with its inherent limitations to determine the prevalence of smoking, with only a few using biological measures. Some of the inconsistent correlations may be attributed to the use of these different smoking definitions and measurements. Fourth, although there are some articles on smoking before lung transplantation, there was only 1 article on correlates or outcomes of posttransplant smoking in lung transplant patients.[29] Although relapse numbers are lower for lung transplant patients, probably reflecting the strict nonsmoking policy and regular assessment of a patient's smoking status pretransplant and posttransplant, they do not equal zero. More specifically, a recent study of Ruttens and colleagues[69] demonstrated that

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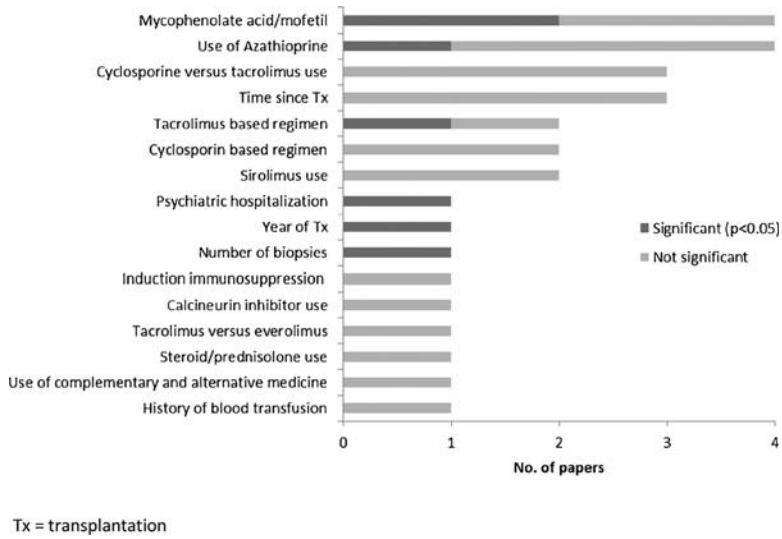

FIGURE 6. Treatment-related correlates of posttransplant smoking assessed by 1 to 4 studies.

12% of lung transplant patients resumed smoking posttransplant. Thus, we believe that more studies are needed to better understand the correlates and outcomes of posttransplant smoking, especially in this vulnerable transplant patient group. Fifth, there were studies that only permitted the effect size estimate to be approximated from less than optimal statistical information (eg, only the sample size, information on the direction of the association, and a *P* value less than or greater than a specified value), leading to less precise estimates of the effect sizes. Moreover, some studies could not be included because the data reported did not permit the calculation of an effect size, probably causing some bias in our review. Although some authors were contacted in case of missing data, we did not receive the information needed to calculate the effect sizes.

This systematic review and meta-analysis might have some methodological shortcomings as well. First, despite the extensive and rigorous systematic review process used, it is possible that relevant papers were missed, bearing in mind that searching for literature is not an exact science. Second, although we included papers in 7 different languages, we had to exclude 10 articles due to a foreign language nobody of the research team could understand. Third, our review is limited to the occurrence of posttransplant smoking, and we did not take into account the severity or duration of posttransplant smoking. Also, by focusing on posttransplant smoking only, we are aware that we did not look at total lifetime exposure to cigarette smoke (ie, both pretransplant and posttransplant), which might be important when investigating impact on outcomes. However, most authors do not clearly distinguish pretransplant versus posttransplant smoking, making it impossible to run separate analyses according to the patients' pretransplant smoking history. These studies were strictly excluded. Moreover, in case that 3 groups were reported (nonsmokers, past smokers, and current smokers), we considered past smokers as nonsmokers, although we did not know whether these patients quit smoking before or after transplantation.

TABLE 3.

Estimated pooled effect sizes as OR generated under a random effects model

			95% CI for the OR		Heterogeneity test				
Factor	No. studies	OR	Lower limit	Upper limit	Q statistic	*P*	τ^2	I^2 (%)	Classic fail-safe N
Socioeconomic-related									
Male sex[26-39]	14	1.33	1.12	1.57	17.20	0.19	0.02	24.42	64
Older age[25-31,33,34,36-39]	13	0.48	0.38	0.62	42.18	<0.001	0.11	71.55	375
Condition-related									
Body mass index[26,27,30,31,36,38,39]	7	0.68	0.52	0.89	12.04	0.06	0.06	50.15	23
Hypertension/being treated with antihypertensive drugs[27,28,31,36,39-41]	7	1.16	0.77	1.75	22.17	0.001	0.19	72.94	—
Diabetes mellitus[27,28,30,31,39-41]	7	0. 52	0.15	1.78	145.59	<0.001	2.52	97.56	—
History of cardiovascular disease[26,28,30,31,39]	5	0.92	0.77	1.09	0.97	0.92	0	0	—
Outcome									
Cardiovascular disease[36,38,40,42-49]	11	1.41	1.02	1.95	16.33	0.09	0.10	38.77	8
Nonskin malignancies[26,40,50-53]	6	2.58	1.26	5.29	18.995	0.002	0.55	73.68	35
Patient survival time[24,26,37,50,54]	5	0.59	0.44	0.79	8.095	0.088	0.05	50.59	32
Patient mortality[26,28-31,50,54,55]	8	1.74	1.21	2.48	42.107	<0.001	0.17	83.38	80

T2, Tau-squared, the variance of the true effect sizes; I2, I-squared, the percentage of variations across studies due to heterogeneity rather than chance.

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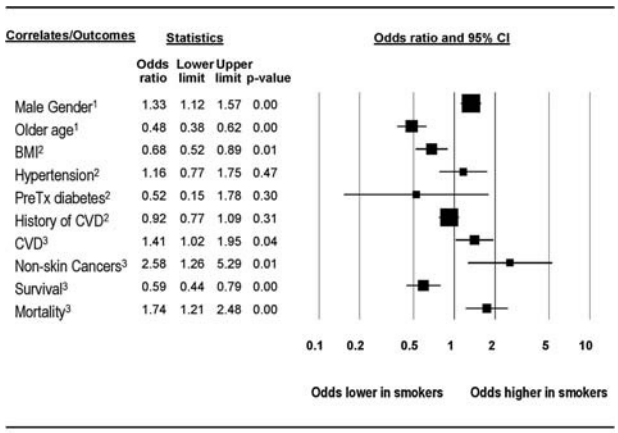


1=Socioeconomic correlate; 2=Condition-specific correlate; 3=Outcome; BMI=Body mass index; PreTx=Pretransplant; CVD=Cardiovascular disease

FIGURE 7. Forest plot of pooled effect size estimates for correlates/outcomes investigated ≥ 5 times.

Implications for Clinical Practice

Despite the limitations of this review, it seems reasonable to conclude that abstinence from cigarette smoking should be strongly encouraged after transplantation, taking into account the association with cardiovascular disease, nonskin malignancies, a shorter patient survival time, and mortality.

Transplant teams have a key role to play in this important area of prevention. They should be encouraged to focus on smoking abstinence as a central theme to discuss with the patient at least at the yearly follow-up check-up. In patients with higher odds for smoking posttransplant (ie, male patients, younger patients, patients with a lower BMI), smoking status may need to be assessed more frequently (every 1 to 3 months).[9]

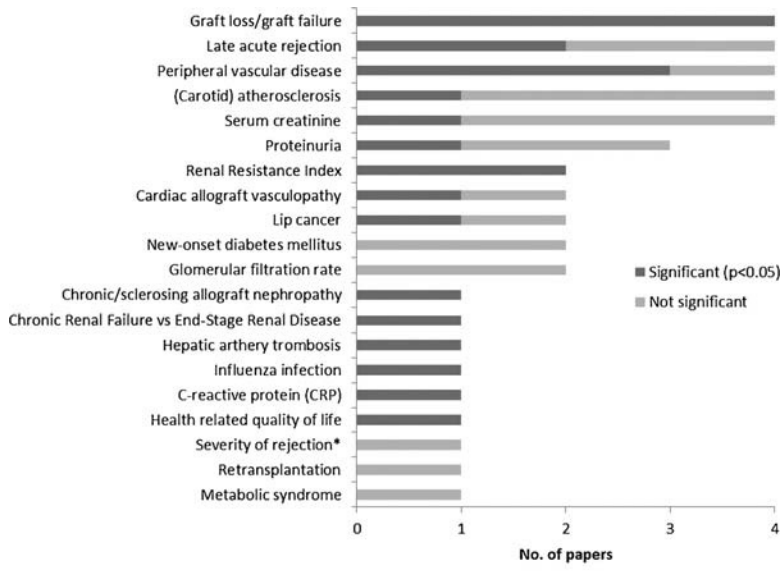
Smoking status can be assessed by self-report and/or biological measures (eg, cotinine measures derived from saliva, urine, and blood or exhaled carbon monoxide). Although cotinine measurements are more objective methods and preferred over self-reported smoking exposure to assess relation of smoking with outcomes in epidemiological studies,[30] self-report is probably the most accessible and cost-effective method to implement in daily clinical practice. Moreover, it has been shown in nontransplant populations that self-reporting of smoking can be a valid measurement method, when used under nonthreatening and open circumstances between healthcare providers and their patients.[70] At the same time, one must be aware that some patients may not admit smoking, because smoking after transplantation remains an ethical issue, and it might be considered ethically justified to deny active smokers a second transplant. Therefore, self-report screening tools must be validated in transplant populations, and where possible, combined with cotinine measurements.[71]

Both the inpatient and the outpatient setting provide an opportunity to promote smoking cessation to active smokers and to encourage continued smoking cessation to past and never smokers. It is important for transplant clinicians to assess patients' motivation to quit smoking or continue smoking cessation and to realize that many patients often make repeated attempts to stop before succeeding in breaking their habit. If motivated patients have difficulties to stop smoking, they can be referred to community smoking cessation services for more intensive behavioral support.

Further, the Institute of Medicine recommends including the behavioral assessment and interventions in the electronic health record, because this has great potential to improve quality, coordination, safety, health outcomes, and overall efficiency in healthcare.[72]

Implications for Future Research

The findings of the current systematic review and meta-analysis also reveal several important implications for future research. First, it is important to emphasize the importance of good and complete reporting. For example, authors should better define smoking, and report important smoking details, such as smoking intensity, duration, and number of pack-years. We also recommend to do separate analyses for pretransplant and posttransplant smoking because correlates and outcomes might be different. Authors also need to report sufficient information to allow calculation of effect sizes. At



* based on published classification systems (Hannover classification)

FIGURE 8. Outcomes of posttransplant smoking assessed by 1 to 4 studies.

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a minimum, they need to report the sample size, exact *P* value, and information on the direction of the association. In addition, future research needs to pay attention to several issues related to the research methodology. For example, studies should be guided by theoretical models to examine the mechanism of how pretransplant and posttransplant factors influence posttransplant smoking and how posttransplant smoking, in turn, may affect outcomes. That way, the relationship of posttransplant smoking with more targeted factors at the patient level, healthcare system–related factors (eg, higher tobacco taxes, antismoking education, bans on tobacco advertising and promotion, policies designed to prevent smoking in public spaces or workplaces), quality of life, and economic outcomes could be explored more. Furthermore, future studies should also use a prospective study design whenever possible to establish a meaningful causal relationship between posttransplant smoking and its correlates and outcomes. Interventions could then be tailored to those at highest risk for smoking posttransplant. Third, given the paucity of data, more studies are needed on correlates and outcomes of posttransplant smoking in lung transplant patients. Fourth, although not the scope of the current review, it would also be helpful to evaluate possible additional risks of electronic cigarette smoking, secondhand smoking, and smokeless tobacco in the transplant population. And fifth, future studies should examine whether smoking withdrawal or cessation after solid organ transplantation has a protective effect against the development of cardiovascular disease.

In conclusion, posttransplant smoking is associated with cardiovascular disease, nonskin malignancies, a shorter patient survival time, and mortality. The association of posttransplant smoking with other outcomes (clinical, economic, and quality of life outcomes) remains to be evaluated. Male patients, younger patients, and patients with a lower BMI are more likely to be smokers. Transplant teams play an important role in routinely assessing patients' smoking status during transplant follow-up by using self-report and/or cotinine measurements, assessing patients' motivation to quit smoking, promoting smoking cessation, and referring motivated patients to community smoking cessation services when necessary.

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